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Sunday December 6th, 2015. Plenary Session (PS 1.1). 4.30 pm to 6.00 pm

Title: PD Related Non Motor Symptoms

Non motor subtypes and Parkinson's Disease

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Abstract

Non motor symptoms (NMS) represent a significant burden in Parkinson's disease (PD) with numerous studies highlighting the importance of NMS both in "pre-motor" phase of PD as well as throughout the disease course. In part this has led the international Parkinson and Movement Disorder Society (IPMDS) task force to attempt a re-definition of PD incorporating NMS and not base the diagnosis solely on motor symptoms. While motor subtypes within PD have been recognized and researched, recent, clinical and neurobiological research suggests the existence of discrete non-motor subtypes in PD, particularly in untreated (drug naïve) and early PD patients. Several independent observers have reported specific "clusters of NMS dominant PD" using a data driven approach in early and untreated PD patients while others have reported on the burden of NMS in untreated PD and specific NMS dominant phenotypes in untreated or treated PD using observational case series based data. In this review we report on specific NMS dominant phenotypes of PD as described in the literature using clinical observational studies and address pathophysiological concepts. A proposal for several NMS subtypes are reported combining clinical reports with, where possible, evidence base supporting probable biomarkers.

Introduction

Why non motor subtypes?

Motor symptoms of Parkinson's disease (PD) such as tremor, bradykinesia and rigidity are the hallmark based on which diagnosis and treatment are started and are now known to be preceded by the “pre-motor” phase of PD largely dominated by a range of different non motor symptoms (NMS) [1-3]

Virtually every PD patient has NMS, which are now widely recognized as an important unmet need in PD [3] and a major determinant of health related quality of life (QoL) of patients with PD and their carers [4]. In a survey by Parkinson's UK, patients listed NMS such as pain, sleep disorders and anxiety ahead of motor problems in clinical importance, and two further studies have outlined the key impact of NMS as declared by patients themselves [3-5].

Despite this importance, little has been done to establish NMS clinical phenotypes in the context of the multi-morbid PD patient even though several workers have reported clinical phenotypes driven by specific NMS such as pain, cognitive problems, apathy and sleep dysfunction. Additionally, cluster analysis from several large early PD and untreated cohorts have all suggested specific NMS dominant or only NMS driven clustering [12-14]. This review aims to highlight these phenotypic variants that have been described within the rubric of Parkinson's disease.

Pathophysiological basis of non-motor subtypes in Parkinson's disease (PD)

NMS based subtyping of PD is plausible from the clinical point of view that in some PD patients, but not all, specific NMS are predominantly expressed, while in others NMS may not be evident or are less relevant. The clinical expression of a range of NMS highlight the fact that the phenotype of PD results from varying rates of Lewy body deposition and

neurodegeneration in PD and represents the effects of widespread brain and peripheral Lewy body pathology instead of a single neural structure affected or the loss of the monoamine neurotransmitter such as dopamine (DA) [3,5]. This convergence of deficits in multiple transmitter systems and pathways, including the cholinergic, noradrenergic, and serotonergic systems, may all be associated with clinical expression of NMS. In addition, glial pathology, neuroimmune responses, and proinflammatory cytokines may also play a key pathogenic role adding to the heterogeneity of PD [5-6]. Furthermore, non-dopaminergic areas in the brainstem may be affected and involved ahead of dopaminergic involvement as recently reviewed by Todorova et al [3, 5-7.] Jellinger has suggested that neuropathological spread of the neurodegenerative process may be initiated via the olfactory bulb and thereafter through the limbic or brainstem areas while spread via the enteric nervous system via the nervus vagus has also been suggested [5-8]. A limbic or brainstem dominant pathophysiological process as proposed by Jellinger [5]. Halliday et al [7] or Beach et al [9] is the basis of our proposal of limbic or brainstem process dominant NMS subtypes as shown in Figure 1. All of these processes would lead to dominant expression of NMS over motor symptoms as also underpinned by the Braak hypothesis of α -synuclein accumulation starting in the lower brainstem and the olfactory bundle well before there is significant involvement of substantia nigra.

NMS subtyping is thus based on the evidence that early and substantial neuronal loss occurs in many non-dopaminergic nuclei in the limbic and brainstem areas, either before or concomitantly with involvement of dopaminergic projections [5, 9-10]. The dorsal motor nucleus of the vagus (DMV) is a key area for control of autonomic signaling responsible for symptoms such as constipation. Neuronal loss in the dorsal motor nucleus of vagus could be as profound as that in the substantia nigra (SN), and large (43-57% loss) cholinergic and

substance P expressing neurons are preferentially lost while tyrosine hydroxylase neurons may be relatively spared in PD [5, 10].

A further contributor in the pathophysiology of non motor subtypes within PD is the age of onset of PD. Preferential Lewy body deposition in the brainstem in young onset PD versus a cortical dominant pathology in late onset PD has been described, the latter being associated with Alzheimer's disease type pathology [11].

It is likely therefore, in these subjects patterns of NMS, dependent on relevant neuropathological involvement of non-dopaminergic areas, will underpin the clinical expression of specific NMS such as sleep problems, apathy, pain, depression/anxiety, ahead of and dominating the typical motor deficit of PD.

Evidence from studies in untreated PD

Untreated PD patients represent a suitable model to study the expression of NMS in comparison to motor symptoms. Erro et al. have conducted a cluster analysis coupled with validated cognitive, motor and non-motor assessments in a untreated PD cohort and found 4 discrete clusters within the cohort termed benign pure motor, benign mixed motor-non-motor, non-motor dominant and motor dominant [12]. The non-motor dominant cluster reported higher urinary dysfunction and a rapid progression rate compared to the benign mixed motor, non-motor cluster.

In the recently reported ONSET-PD study, the authors highlighted specific non motor clusters of PD ranging from cognitive and mood clusters to sensory, RBD dominant and autonomic dysfunction related cluster further supporting our attempt of NM subtyping of PD [13]. Studies have also identified specific clinical phenotypes in untreated PD underpinned by NMS such as sleep dysfunction, cognitive and neuropsychiatric disturbances (depression, apathy), fatigue, dysautonomia, pain and olfaction recently reviewed by Zis et al [14]. These

observations fit well with the neuropathological studies, which have suggested a differential rate of neuronal degeneration and Lewy body deposition in the non-dopaminergic brainstem and limbic areas in PD, with consequent expression of a variety of related NMS.

The Literature descriptions of specific NMS dominant subtypes of PD:

A proposal of at least six different NMS dominant clinical phenotypes within PD mainly in early and untreated phase has been proposed based on clinical observation and in this review we discuss the patterns that have been reported and published so far [15].

Park Cognitive

Clinically the Park Cognitive subtype predominantly presents with cognitive impairment even at an early stage.

Neuropathologically, this subgroup may represent the late onset pattern of Lewy body deposition [7]. The patients are likely to present with mild cognitive impairment (MCI), which may progress to frank dementia (Figure 1). The condition overlaps clinically with dementia with Lewy bodies (particularly when there is fluctuating cognitive state however, Park cognitive shows sustained levodopa responsiveness) and Alzheimer's disease. The use of thioflavin ligand based positron emission tomography (PET) scans, amyloid scans, cholinergic imaging or cortical thinning (functional MRI) may help to further refine the clinical classification [16].

Early dementia – probably reflecting a high cortical Lewy body load, occurs but importantly the patients retain levodopa responsiveness in part. Clinical studies by Williams-Grey et al. suggest that in this cohort (Park Cognitive) impaired semantic fluency (less than 20 words in 90 sec) and inability to copy an intersecting pentagons figure are predictive of dementia [17].

Clinical differences between amnestic and non-amnestic subtypes within the PD-MCI have been reported and Microtubule-associated protein tau (MAPT) H1/H1 genotype may be a molecular biomarker [17-18] (Table 1a).

Park Apathy

Clinically the Park Apathy subtype score high on apathy scales, and specific apathy dominant phenotype in untreated PD excluding the possibility of dopamine agonist withdrawal syndrome as a confounder [18] (Table 1b). There are also high rates of cognitive impairment as well as anhedonia in these cases. Current perception suggests apathy in PD may be a dopamine responsive NMS. Clinically, some patient might present with severe apathy but mild Parkinsonism and need treatment in spite of their mild motor impairment.

Park Depression/Anxiety

Clinically the Park depression/anxiety phenotype might occur in both late and early onset PD with both depression and anxiety and it is important to consider these symptom in the context with motor fluctuations. This description is based on the clinical analysis of cases as reported in the Prospective Study of Mood States in Parkinson's Disease (PROMS-PD) study [19-20]. Brainstem as well as the limbic involvement could be responsible (Figure 1). The clinical protocol for the PROMS-PD study specifically addressed fluctuation related changes in depression and anxiety states to account for non motor fluctuations as well as exclusion of confounders such as generalized anxiety states or comorbid illnesses.

Three different subtypes namely anxious depressed, depressed, anxious as well as psychologically healthy subtype have been described (Table 1c) and there is a correlation with cognitive impairment and an overlap with the Park Cognitive phenotype (Figure 1).

Reduced catecholaminergic (^{11}C -RTI-32) binding has been reported in depressed versus non-depressed PD patients and reduced binding in ventral striatum, medial thalamus, and locus ceruleus was associated with severity of anxiety (but not depressive) symptoms [21].

Park Sleep

Clinically the phenotype could be divided into two subtypes (Figure 1). The first type is characterized by excessive daytime sleepiness (EDS) (high scores on the Epworth sleepiness scale (ESS)) and clinically complaints of severe somnolence. Some may have narcolepsy without cataplexy and may be particularly susceptible to the sedating effects of dopamine 3 receptor agonists. This subtype is at particular risk of sudden onset of sleep during initiation and up-titration of dopamine agonist therapy. Abnormalities in the central orexin pathway and loss of orexin containing cells in hypothalamus may underpin this subtype.

The second type presents with rapid eye movement (REM) behaviour disorder (RBD), a sleep disorder subtype characterized by motor enactment of violent intrusive and aggressive dreams during REM sleep (Table 1d). RBD is typically manifested as a pre-motor phenomenon and can be linked to synucleinopathies .

The EDS specific phenotype has been independently described by various authors [22].

A central brainstem generator in the midbrain area centered around the pedunculopontine area and sublaterodorsal nucleus has been suggested in RBD and supported by imaging studies showing reduced fractional anisotropy as well as reduced midbrain tegmental ^{18}F -dopa uptake [23]. Imaging studies have also identified and supported the concept of specific sleep subtypes. Recent studies using ^{11}C -labeled 3-amino-4-(2-dimethylaminomethyl-phenylsulfanyl) benzonitrile (^{11}C -DASB) PET, a serotonin transporter marker, have suggested specific deficits in serotonergic neurotransmission in the dorsal and ventral raphe nucleus (arousal areas) in patients with EDS but not in controls or those without EDS [24].

Histopathological studies suggest a deficiency of orexin containing neurons in somnolent PD cases but not controls, and this has also been suggested by low orexin levels in brain ventricular fluid samples, although data from lumbar puncture samples are contradictory [3].

Park Pain

Clinically the Park Pain subtype express a range of different pain syndromes which dominate the clinical picture; this possibly represents the phenotype previously described as “painful Parkinson’s disease” by Quinn et al in 1986 [27].

The Park Pain subtype has a higher risk to develop disproportionate pain during the progression of PD compared to the motor severity of disease. Several variants of pain such as nociceptive and neuropathic, central, peripheral, radicular and fluctuation-related, are described and an unexplained lower limb pain syndrome is the only subtype that has been well described so far (Table 1e) [28]. Refinement of the population studied have been aided by a new pain classification now published as a validated pain scale for PD which have allowed exclusion of secondary pain in PD as far as possible.

Park Fatigue

There is now growing evidence that fatigue indeed is an independent NMS separate from apathy or sleep dysfunction. Several patient report based publications have also identified fatigue as a major patient reported problem where there is no depression or somnolence.

Clinically the Park Fatigue subtype suffers from severe fatigue, a sense of exhaustion as defined and assessed by recommended scales of the international Parkinson and Movement Disorder Society (IPMDS) task force. At least two studies have identified fatigue to be a major NMS in untreated PD as well as early PD [14, 25]. The distinction between central and peripheral fatigue can also overlap, but recent studies suggest that this subtype can be independently recognized using specific PET studies showing central limbic serotonergic

deficit separate from the raphe serotonergic deficit seen in Park Sleep (EDS) subtype [26]. In this study, patients with Park fatigue, who were matched with a healthy control group as well as PD patients without fatigue in terms of motor scores, depression scores as well as excessive daytime somnolence assessments, showed a specific limbic serotonergic deficit.

Park autonomic

Clinically the Park Autonomic subtype presents with a variety of autonomic dysfunctions including sexual dysfunction, constipation to urinary frequency, urgency and nocturia as their predominant symptoms. Broadly the phenotypes could be subdivided to:

- Gastro-intestinal symptoms dominant and
- Genito-urinary symptoms dominant (dominated by urinary symptoms) (Figure 1).
- Adrenergic dysfunction dominant (clinically dominated by postural hypotension, post-prandial hypotension and also post exercise hypotension) (reviewed in [29]).

Neuropathologically, a dominant noradrenergic deficit is likely to be the key and a recent review has highlighted the role of noradrenergic deficit in PD and the need for specific noradrenergic treatment [29]. These patients are also likely to represent the PD with autonomic failure (as opposed to MSA) phenotype and while the clinical picture may be dominated by postural hypotension, symptoms secondary to postprandial hypotension such as post-meal dizziness and excessive somnolence or post exercise hypotension are also evident. [29]. Iodine-131-meta-iodobenzylguanidine (MIBG) cardiac scans can detect cardiac sympathetic denervation (equivalent to a non visualization of the heart) even before the onset of motor symptoms in PD, while in many other cases loss of cardiac sympathetic innervation appears to progress approximately concurrently with the movement disorder or in some patients can be a late finding. In terms of NMS, apart from postural hypotension and features

of the adrenergic variants, cardiac MIBS abnormalities have also been implicated in fatigue related to PD.

In addition Sharma and colleagues have described a phenotype characterized by a weight loss combined with severe olfactory dysfunction and dyskinesia in PD as shown in Table 1f (Park weight phenotype)[30].

The problems of non-motor subtyping

As PD is a heterogeneous disorder there is considerable possibility that these subtypes will overlap and are likely to be present only in a proportion of patients. Comparable with the instability of motor subtypes, non-motor subtypes will change throughout the course of disease and at the end several types will merge and overlap. As such we accept that the classification is a simplification with heterogeneity and overlapping probably existing within these proposed major subtypes.

Selection bias within the samples examined may be considered a problem, however, clustering based as well as clinical observational phenotyping based papers have been in mostly in untreated or early PD patients and as such with no major selection bias because the basic inclusion is a diagnosis of motor PD. For instance Park cognitive or Park pain types have been based on symptom expression from a population based PD sample presenting to the clinic and not a sample specifically screened and selected for non motor studies.

NMS subtyping is an important advance in the translation of pathophysiology advances in PD to clinical practice and we would like to suggest that NMS subtyping would enrich the design of clinical trials and recruitment of patients as well improve the knowledge about the natural history of PD, which thus far have only addressed motor symptoms. For instance:

1. A Park sleep subtype with a narcoleptic variant may be intolerant to D3 active dopamine agonist and vigilance would be required especially when such patients are on DA and driving. This could be applied to patient selection for related clinical trials.
2. A Park Fatigue subtype could be an ideal group to attempt a clinical trial of serotonin receptor agonist agent rather than selecting a general cohort of PD based on Pavese et al study [26]
3. A Park pain phenotype would be a good candidate for opioid based therapies (PANDA study (ClinicalTrials.gov Identifier:NCT01439100) based on opioid versus placebo therapy in Parkinson associated pain has started

As with most clinical observations in PD there is likely to be overlap as indeed between the well established motor subtypes; for instance, many akinesia dominant phenotypes may develop tremor or postural instability subtype. The success of our proposed NMS subtypes can only be validated by natural history studies and while the evidence (pathophysiological as well as from a biomarker point of view) is strong for some NMS subtypes (cognitive, adrenergic, sleep) for others such as pain it currently is rather weak.

Conclusion

NMS subtyping in PD is a new concept and as shown in this paper is clinically relevant and possible. The process emphasizes the value of incorporating NMS as an obligatory clinic assessment which aims to ensure that NMS are not missed in the clinic currently dominated by motor assessment and leads to sub-optimal care. Subtyping of clinically heterogeneous conditions is possible and regarded as routine clinical practice in conditions such as multiple sclerosis, motor neuron disease, and epilepsy, and this has now led to subtype-directed treatment strategies in some of these conditions. We feel, this is also possible, and desirable, in a highly clinically heterogeneous condition such as PD and in future, may lead to

development of focused NMS outcome based clinical trials in carefully selected patients, a key unmet need in PD as well as shed light on NMS based natural history pattern in PD.

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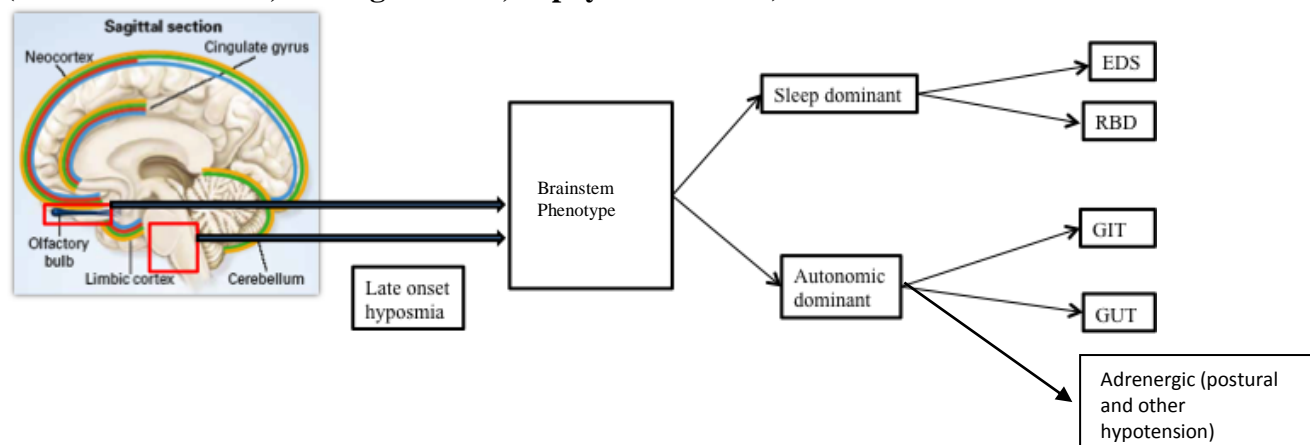
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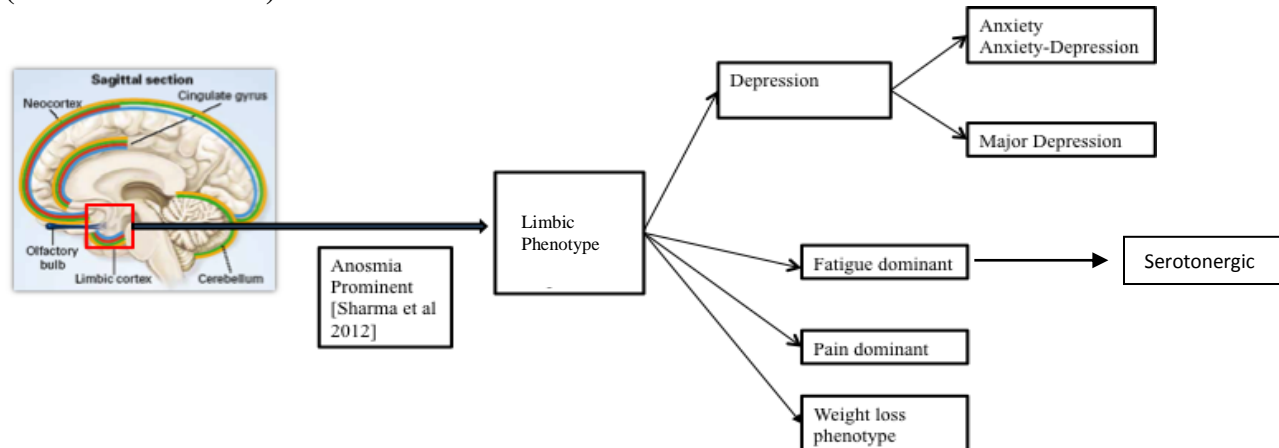
Brainstem ± Olfactory route

(Braak et al. Ref 14, Jellinger. Ref 7, Espay et al. Ref 29)



Olfactory route

(Beech et al. Ref 11)



Cognitive (older age of onset)

(Halliday et al. Ref 9, Weintraub et al 2015)

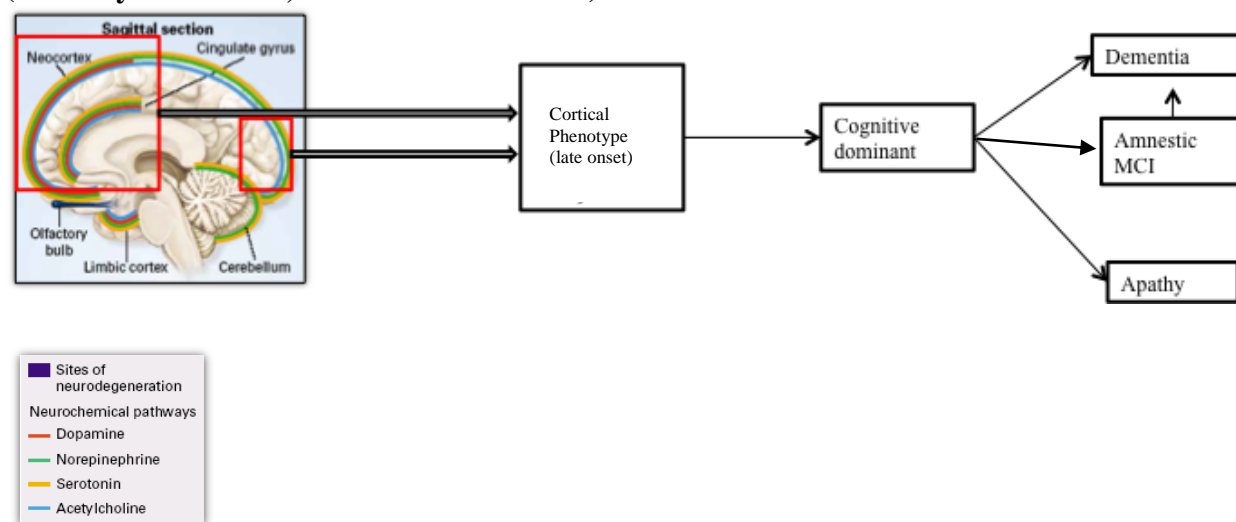


Figure 1: A proposed concept illustrating the pathophysiological, clinical and possible biomarker based concepts underpinning non motor subtypes in PD. The sagittal section

diagrams show possible routes of spread of the pathophysiological process in PD as published. The cognitive phenotype is underpinned by age of onset. Adrenergic (autonomic dominant) and serotonergic (fatigue) represent reports of specific neurochemical deficits underlying these subtypes as reported in literature (references 29 and 26)

EDS= Excessive daytime sleepiness ; RBD= REM sleep behavior disorder; GIT= Gastro intestinal tract; GUT= Genito urinary symptoms; MCI= Mild cognitive impairment.

Table 1 Different possible subtypes within Parkinson's disease as described in literature**a) Cognitive subtype in Parkinson's disease [20]**

- Older age (≥ 72 years)
- Non-tremor dominant motor phenotype
- Unified Parkinson's Disease Rating Scale (UPDRS) score ≥ 25
- Poor semantic fluency score (<20)
- Lower pentagon copying score ($0 < 1 < 2$)
- Microtubule-associated protein tau (MAPT) H1/H1 genotype

b) Apathy subtype in drug naïve Parkinson's disease [18]

- High scores on apathy rating scales
- Relatively severe motor symptoms
- Concomitant depression
- Lower cognitive status
- Fatigue
- Anhedonia and response to dopaminergic drugs

c) Depression/Anxiety subtypes in Parkinson's disease [19-20]**1. Anxious depressed subtype**

- Younger age
- Early age of onset
- Long disease duration
- Significant motor disability and higher Unified Parkinson's Disease Rating Scale (UPDRS) scores
- Postural instability/falls subtype
- Motor fluctuations
- Significant cognitive impairment
- Markedly increased levels of anxiety and depression

2. Depressed subtype

- Older age
- Late age of onset
- Shorter duration of Parkinson's disease
- Postural instability gait disturbance (PIGD) subtype
- Significant motor impairment and disability

- Motor fluctuations
- High levels of depression

3. Anxious subtype

- Younger age
- Young age of onset
- Advanced disease with motor fluctuations
- Postural instability gait disturbance (PIGD) subtype
- Cognitive impairment
- High levels of anxiety

d) REM sleep behavior disorder subtype in Parkinson's disease [22]

- Symmetric disease onset
- Increased periods of freezing
- Autonomic dysfunction - Prone to higher prevalence and severity of orthostatic symptoms
- Higher rate of depression
- Visual hallucinations
- Male gender
- Older age
- Non tremor dominant subtype/ akinetic rigid syndrome
- Increased frequency of falls
- Depression
- Higher Hoehn and Yahr motor stage
- Impairment of colour vision

e) Lower limb pain subtype in Parkinson's disease [27-28]

- Male>female
- Across all age groups
- Moderate to advanced Parkinson's disease
- Pain in anterior proximal aspect of lower limb, described as internal pain
- Lack of effect of physiotherapy
- Unrelated to non motor fluctuations
- Responsive to opiates

f) Park weight subtype (combined with olfactory dysfunction and dyskinesia) in Parkinson's disease [30]

1. Phenotype A – More severe loss of olfaction (anosmia)

- Higher initial body weight
- Weight loss with progression of disease
- Higher risk of dyskinesias
- More severe neurodegeneration
- Longer premotor disease duration

2. Phenotype B – Less loss of olfaction (hyposmia)

- Lower initial body weight
- No weight loss/ weight gain with progression of disease
- Lower risk of dyskinesias
- Slower neurodegeneration
- Shorter premotor disease duration